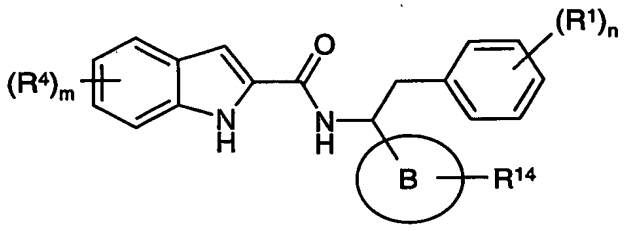
Claims

1. A compound of formula (1):



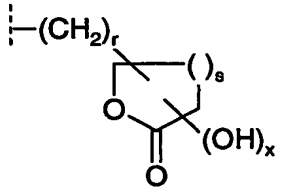
(1)

wherein:

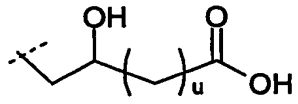
n is 0, 1 or 2;

m is 0, 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N*,*N*-(C_{1-4}alkyl)$_2$amino, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and groups of the formula A or A':



(A)



(A')

wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and us is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^4 is independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy and C_{1-4}alkanoyl;

B is phenyl or heterocyclyl;

R^{14} is selected from hydrogen, halo, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), C_{1-4}alkoxy, cyano, cyano(C_{1-4})alkyl, -COR^3, (R^2)(R^3)NCO-, and (R^2)(R^3)NSO_2-;

R^2 and R^3 are independently selected from C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl (optionally substituted with 1 or 2 R^8 groups), $-OR^8$ and R^8;

R^8 is independently selected from hydrogen, 2,2-dimethyl-1,3-dioxolan-4-yl, heterocyclyl (optionally substituted on ring carbon or ring nitrogen by 1 or 2 groups selected from hydrogen, nitro, halo, cyano, hydroxy and C_{1-4}alkyl), (heterocyclyl)C_{1-4}alkyl (wherein the heterocyclyl is optionally substituted on ring carbon or ring nitrogen by 1 or 2 groups selected from hydrogen, nitro, halo, cyano, hydroxy and C_{1-4}alkyl), aryl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen by 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), -N(OH)CHO, $-CH_2CH(CO_2R^9)N(R^9R^{10})$, $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$ and $-(CH_2)_uCH(NR^9R^{10})CO_2R^9$ (wherein u is 1, 2 or 3);

R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, 2,2-dimethyl-1,3-dioxolan-4-yl, aryl (optionally substituted by 1 or 2 substituents selected from hydrogen, nitro, halo, hydroxy and C_{1-4}alkyl) and C_{1-4}alkyl substituted by R^{13} ; or

R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N,N*-(C_{1-4}alkyl)$_2$amino, carbonyl, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_f$(C_{1-4})alkyl (wherein f is 0, 1 or 2), -N(OH)CHO, $(R^{11})(R^{12})NCO-$, $(R^{11})(R^{12})NSO_2-$, $-COCH_2OR^{11}$ and $(R^{11})(R^{12})N-$;

R^{13} is selected from hydroxy, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_d$ (wherein d is 0, 1 or 2), -N(OH)CHO, $-C(O)N(R^{11})(R^{12})$, $(R^{11})(R^{12})NSO_2-$, $-COCH_2OR^{11}$ and $(R^{11})(R^{12})N-$;

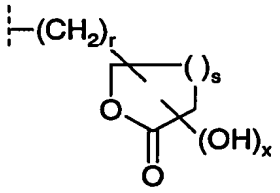
R^{11} and R^{12} are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl and C_{1-4}alkyl$S(O)_e$ (wherein e is 0, 1 or 2);

or a pharmaceutically acceptable salt or pro-drug thereof.

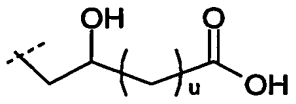
2. A compound of the formula (1) as claimed in claim 1, wherein

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, cyano, nitro, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl and groups of the formula A or A':



(A')



(A")

wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

B is heterocyclyl;

R^{14} is selected from is selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, $-COR^3$, $(R^2)(R^3)NCO-$, and $(R^2)(R^3)NSO_2-$;

R^2 and R^3 are independently selected from C_{1-4}alkyl (substituted by 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, C_{1-4}alkyl (substituted by R^8), $-OR^8$ and R^8;

R^8 is independently selected from hydrogen, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, morpholino, pyridyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, 4-methylpiperazino, C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen by 1 or 2

groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkylS(O)$_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), -$CH_2CH(CO_2R^9)N(R^9R^{10})$, -$CH_2OR^9$, -$(R^9)(R^{10})N$-, -$COOR^9$, -$CH_2COOR^9$, -$CH_2CONR^9R^{10}$, and -$CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano) and C_{1-4}alkyl substituted by R^{13}; or

R^9 and R^{10} can together with the nitrogen to which they are attached form 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, nitroso, cyano, isocyano, amino, *N*-C_{1-4}alkylamino, *N*,*N*-(C_{1-4})$_2$alkylamino, carbonyl, C_{1-4}alkoxy, heterocyclyl, C_{1-4}alkanoyl, and C_{1-4}alkylS(O)$_f$(C_{1-4})alkyl (wherein f is 0, 1 or 2);

R^{13} is selected from C_{1-4}alkoxy, furyl (optionally substituted on carbon by 1 or 2 nitro groups), thienyl (optionally substituted on carbon by 1 or 2 nitro groups), morpholino, furyl(C_{1-4})alkyl (wherein furyl is optionally substituted on carbon by 1 or 2 nitro groups), thienyl(C_{1-4})alkyl (wherein thienyl is optionally substituted on carbon by 1 or 2 nitro groups), 1,2,4-oxadiazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), pyrazinyl, piperazinyl, C_{1-4}alkylS(O)$_d$(C_{1-4})alkyl (wherein d is 0, 1 or 2);

m is 1 or 2;

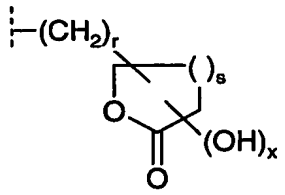
R^4 is hydrogen or halo;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

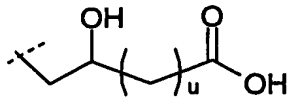
3. A compound of the formula (1) as claimed in claim 1, wherein:

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and groups of the formula A or A':



(A')



(A")

wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

B is heterocyclyl;

R^{14} is selected from hydrogen, halo, cyano, C_{1-4}alkoxy, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups provided that when there are 2 hydroxy groups they are not substituents on the same carbon) and cyanoC_{1-4}alkyl;

m is 1;

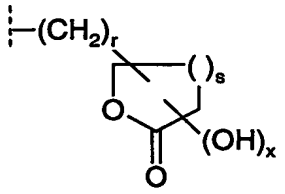
R^4 is chloro;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

4. A compound of the formula (1) as claimed in claim 1 wherein:

n is 1 or 2;

R^1 is independently selected from hydrogen, halo, nitro, hydroxy, C_{1-4}alkyl and R^1 is of the formula A or A':



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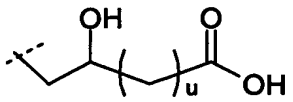


(A")

wherein x is 0 or 1, r is 0, 1, 2 or 3, s is 1 or 2 and u is 1 or 2; provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

B is phenyl;

R^{14} is selected from is selected from C_{1-4}alkyl, cyano(C_{1-4})alkyl, -COR^3, $(R^2)(R^3)NCO$-, and $(R^2)(R^3)NSO_2$-;

R^2 and R^3 are independently selected from C_{1-4}alkyl, C_{1-4}alkyl (substituted by R^8), – OR^8 and R^8;

R^8 is independently selected from hydrogen, heterocyclyl (optionally substituted on carbon or nitrogen by 1 or 2 groups selected from nitro, halo, hydroxy, cyano and C_{1-4}alkyl), (heterocyclyl)(C_{1-4})alkyl (optionally substituted on carbon or nitrogen by 1 or 2 groups selected from nitro, halo, hydroxy, cyano and C_{1-4}alkyl), aryl (optionally substituted by 1 or 2 groups selected from nitro, halo, cyano, hydroxy and C_{1-4}alkyl), C_{1-4}alkyl, C_{2-4}alkenyl, cyclo(C_{3-8})alkyl, C_{1-4}alkoxy, cyano(C_{1-4})alkyl, amino(C_{1-4})alkyl (optionally substituted on nitrogen by 1 or 2 groups selected from hydrogen, C_{1-4}alkyl, hydroxy, hydroxy(C_{1-4})alkyl, dihydroxy(C_{1-4})alkyl, aryl and aryl(C_{1-4})alkyl), C_{1-4}alkyl$S(O)_c$(C_{1-4})alkyl (wherein c is 0, 1 or 2), $-(CH_2)_uCH(CO_2R^9)N(R^9R^{10})$ (wherein u is 0, 1 or 2), $-CH_2OR^9$, $(R^9)(R^{10})N-$, $-COOR^9$ and $-CH_2COOR^9$, $-CH_2CONR^9R^{10}$, $-CH_2CH_2CH(NR^9R^{10})CO_2R^9$;

R^9 and R^{10} are independently selected from hydrogen, C_{1-4}alkyl (optionally substituted by 1 or 2 hydroxy groups), C_{5-7}cycloalkyl (optionally substituted by 1 or 2 hydroxy groups), C_{2-4}alkenyl, cyano(C_{1-4})alkyl, and phenyl (optionally substituted by 1 or 2 groups selected from nitro, halo, hydroxy and cyano);

m is 1;

R^4 is chloro;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

5. A compound of the invention which is:

methyl (*S*)-5-{1-[(5-chloro-1*H*-indol-2-ylcarbonyl)amino]-2-phenylethyl}oxazole-4-carboxylate;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

6. A pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or inivivo hydrolysable ester thereof, as claimed in any one of claims 1 to 5 in association with a pharmaceutically-acceptable diluent or carrier.

7. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 5, for use in a method of treatment of a warm-blooded animal such as man by therapy.

8. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 5, for use as a medicament.

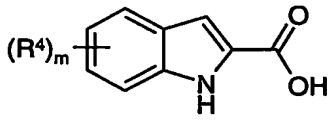
9. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 to 5, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

10. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 5, in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

11. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of claims 1 to 5, in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

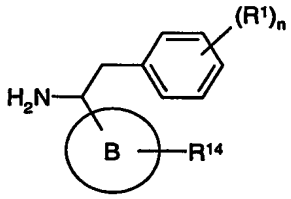
12. A process for the preparation of a compound of formula (1) as claimed in claim 1, which process comprises:

reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):



(3)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or in-vivo hydrolysable ester.